Safety Data Sheet

Vinblastine sulfate

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS TOXIC, TERATOGENIC, AND EMBRYOTOXIC. IT IS READILY ABSORBED THROUGH THE INTESTINAL TRACT. IT MAY IRRITATE THE SKIN AND INDUCE SENSITIVITY. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, DRINK MILK OR WATER. INDUCE VOMITING. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. SEE CASTEGNARO ET AL. (1985) FOR DETAILS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Vinblastine (VLB) is an alkaloid isolated from the leaves, bark, or stem of the Madagascar periwinkle Catharanthus roseus G. Don (formerly called Vinca rosea Linn). It is a dimer of an indole (catharanthine) and a dihydroindole (indoline, vindoline) moiety. The sulfate (VLB), the form in which it is used in medical practice,

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is a white to slightly yellow hygroscopic crystalline compound, soluble in water and methanol. It is highly toxic in all mammalian species tested (parenteral and oral LD50 in the mg/kg range) though somewhat less so than the closely related vincristine. Exposure of skin and eyes may produce vesication. Its major use is as an antineoplastic against Hodgkin's disease, breast cancer, renal and Kaposi's sarcoma, and others but it is not particularly effective against acute leukemias. It also increases the effectiveness of other antineoplastics when combined with them in nontoxic doses. Its dose-limiting effects are due to interference with the hematopoietic system. Its mode of action is an inhibition of the mitotic processes due to strong binding to the protein tubulin in mitotic spindles, with formation of cytoplasmic inclusion bodies ("microtubule crystals") leading to inhibition of biosynthesis of DNA, RNA, and protein.

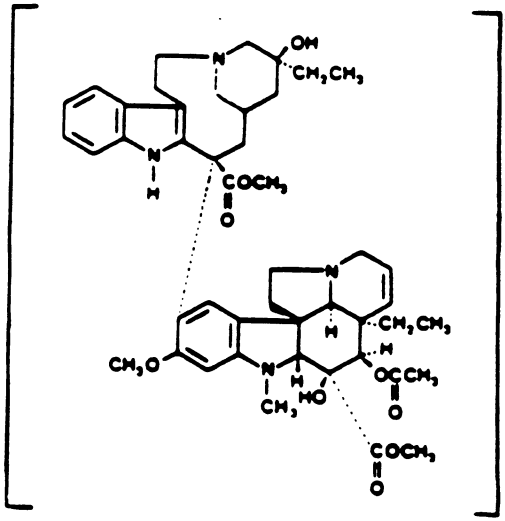
General reviews include Burns (1972), Creasey (1975), IARC (1981).

B. Chemical and Physical Data

1. Chemical Abstract No.: 865-21-4 for the free base; 143-67-9 for the sulfate.

2. Synonyms: Vincaleukoblastine sulfate (1:1);[A] VLB; VLB sulfate. Trade names: Exal; 29060-LE; NSC 49842; Velbe; Velban. For systematic name see Chemical Abstracts, 9th Collective Index, p. 40237 CS.

3. Chemical structure and molecular weight:



Catharanthine moiety

$\cdot H_2SO_4$ - - - - - - - -

Vindoline moiety

free base: $C_{46}H_{59}N_4O_9$; m.w. 811
sulfate: $C_{46}H_{59}N_4O_9.H_2SO_4$; m.w. 909

[A] Chemical Abstracts name, used for listing in 7th Decennial Index and subsequently.

Density: No data.

Absorption spectroscopy: Ultraviolet maxima at 214 and 262 nm; the 262 nm maximum is shifted to longer wavelengths in alkaline and to shorter wavelengths in acid solution. Infrared and NMR spectral data have been tabulated (Burns, 1972).

Volatility: No data. VLB may be regarded as essentially nonvolatile.

Solubility: VLB is soluble in water (1 in 10), ethanol (1 in 12,200), chloroform (1 in 50), and methanol; insoluble in ether (IARC, 1981).

Description: White to slightly yellow, odorless, crystalline or amorphous powder. Very hygroscopic. pK_as: 5.4, 7.4.

Boiling point: No data; melting point: 284-285°C with decomposition for monohydrate.

Stability: Dry VLB is heat-stable in the absence of atmospheric oxygen; decomposition is 2% in sealed ampoules in an inert atmosphere at 100°C for 16 hours, but 50% in air under the same conditions. Aqueous solutions are heat-stable at their normal pH of 4.5 but considerable decomposition occurs at pH 2 (Burns, 1972). Since the free base is stated to be unstable, the same probably applies to alkaline solutions of VLB. VLB, like other indole compounds, is probably susceptible to ultraviolet radiation; while there are no quantitative data on the subject, it is recommended that tissue preparations for analytical purposes be carried out under fluorescent light (without an ultraviolet component) or in the dark (Owellen et al., 1981). It is noteworthy that the strong adsorption to plastic and cellulose materials noted for vincristine sulfate is not encountered with VLB (Butler et al., 1980; Benvenuto et al., 1981).

Chemical reactivity: The two ring structures of VLB are subject to the usual reactions such as reduction or acylation of the free OH groups, deacylation of acetyl groups, substitution of the secondary amino group, etc. Such reactions have been used in synthesis of other congeners of the Vinca alkaloids. The effects of some of these reactions on biological activity have been described (Creasey, 1975; Sieber et al., 1976).

Flash point: No data.

Autoignition temperature: No data.

Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazards Data

1. VLB is likely to be inactivated under conditions of fire. Because of its vesicant action it is recommended that fire-fighting personnel wear protective clothing and face masks.

2. Flammability is likely to be low.

3. Conditions contributing to instability are exposure to acid or alkali, oxidants, elevated temperatures, or ultraviolet light.

4. Hazardous decomposition products under conditions of fire are nitrogen and sulfur oxides (Sax, 1984).

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving VLB.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).

2. Decontamination: Turn off equipment that could be affected by VLB or the materials used for clean up. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Consult Castegnaro et al. (1985) for details concerning decontamination of surfaces, glassware, and animal cages.

3. Disposal: It may be possible to decontaminate waste streams containing VLB before disposal. For details, see Castegnaro et al. (1985). No waste streams containing VLB shall be disposed of in sinks or general refuse. Surplus VLB or chemical waste streams contaminated with VLB shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing VLB shall be handled and

packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing VLB shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with VLB shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing VLB shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: For information on storage stability see B10. Solid VLB may be stored at room temperature in sealed ampoules with inert atmosphere in the dark.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: No data.

2. Analysis:

   a. Introductory notes.

      (1) Analytical procedures prior to 1971 have been received by Burns (1972).

      (2) In general, analytical methods developed for VLB are also applicable to vincristine sulfate, and vice versa. Therefore, all methods developed for either compound are quoted below.

   b. Sample extraction and preparation: It is important that tissue extractions be carried out at acid pH since structural changes and partial destruction of the Vinca alkaloids may occur at alkaline pH. A method for extraction with 95% ethanol at pH 4.9 has been described (Houghton et al., 1983).

   c. Analysis: The two principal methods are based on bioassay or radioimmunoassay; both have advantages and disadvantages. Bioassay is the less sensitive of the procedures (lowest detectable concentration is 0.01 µg/ml plasma or 0.1 µg/g tissue) and measures both intact alkaloid and active metabolites, being based on mitotic arrest (Dixon et al., 1969; Aoshima and Sakurai, 1973; Kipp and Barendsen, 1981). None of these reports mentions the presence or absence of cross reaction with, or interference by, other antineoplastics which may be present when they are used concomitantly

are used concomitantly in clinical practice. Radioimmunoassay (RIA) likewise does not distinguish between the alkaloid and its deacetyl derivative which is an active metabolite (Owellen et al., 1977).[A] Several such procedures have been described (Owellen et al., 1977; Teale et al., 1977; Langone et al., 1979; Sethi et al., 1980; Owelle et al., 1981). The sensitivity is of the order of 2 ng VBL/ml. Most authors mention absence of interference by non-Vinca alkaloid antineoplastics. It is noteworthy that the procedure described by Langone et al. (1979) is reported to yield antibodies which are 200 times more sensitive for vincristine sulfate than for VLB. Because of the cost of radiolabeled antigen and of measuring equipment, Hacker et al. (1984) have developed an enzyme-linked immunoabsorbent assay (ELISA) which is based on conjugation of VLB with alkaline phosphatase, capable of detecting 5 pg of VLB or vincristine. For measurement of possible metabolites, Castle and Mead (1978) have used high-pressure liqui chromatography.

F. Biological Effects (Animal and Human)

1. Absorption: VLB is absorbed and produces biological effects on parenteral (intravenous, the usual clinical method, and intraperitoneal) injection. It is slightly less effective on ingestion. It acts as a vesicant and may produce contact dermatitis as a result of handling or by extravasation due to needle slipping during treatment; however, it is not known whether systemic toxic effects are produced by this route

2. Distribution and pharmacokinetics: Intravenous VLB is cleared from plasma relatively quickly in the rat, dog, or man. This clearance has been described as biphasic for the dog ($t_{1/2}$ 17-38 minutes and 3-5 hours; Creasey et al., 1975) and as either biphasic ($t_{1/2}$ 4-5 and 185-195 minutes; Owellen and Hartke, 1975) or triphasic ($t_{1/2}$ 3.9, 53, and 1173 minutes; Owellen et al., 1977) for man, resulting in either a two- or three-compartment system. Other pharmacokinetic data, supporting a two-compartment open system, have been published for the rhesus monkey (Sethi et al., 1984). There are few data on tissue distribution of VLB following its disappearance from plasma

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[A]Since all RIA methods depend on the use of tritiated VLB, the production and radiopurity of this compound is of some importance. Usually VLB is tritiated by the Wilzbach procedure in which VLB is exposed to tritium gas. This results mainly in labeling of the ring structure but also produces ill-defined radioactive impurities (Bees and Richards, 1964; Owellen and Hartke, 1975). A more specific method of preparation has been described by Castle et al. (1976).

except that a considerable amount is bound to formed elements of blood (leukocytes, platelets) (Creasey et al., 1975; Owellen and Hartke, 1975; Gout et al., 1978).

Metabolism and excretion: The metabolism of VLB is not well understood, mainly due to analytical difficulties related to the low tolerated dosages and the instability of VLB in analytical systems. The only metabolite which has been identified is the deacetyl derivative which is more toxic than VLB (Owellen et al., 1977), though other metabolites are also formed. In the dog, the total amount of radioactivity excreted was 12-17% in urine and 30-36% in feces, mainly in the form of unchanged VLB (Creasey et al., 1975).

Toxic effects: The acute LD50 of VLB is about 3, 10-17, and 33 mg/kg by the intraperitoneal, intravenous, and oral routes, respectively. The rat shows an intravenous LD50 of 2.9 mg/kg (Cosgriff, 1968; Todd et al., 1976; Houchens et al., 1977). The maximum tolerated dose in man is 150 µg/kg (Gout et al., 1978) which is six times higher than that for vincristine.

The toxic effects in man and animals have been reviewed (De Conti and Creasey, 1975; Goodman and Gilman, 1985) and contrasted with those of vincristine (Johnson, 1968; Gout et al., 1978). The main (dose-limiting) effect of VLB is leukopenia although at high doses the peripheral neurotoxicity characteristic for vincristine is also observed. On intradermal injection VLB produces soft tissue necrosis in the guinea pig (Barr et al., 1981) and mouse (Dorr and Alberts, 1985).

The mechanism of toxic and antineoplastic action of VLB is cell damage by mitotic arrest. VLB binds strongly to tubulin, a protein constituent of mitotic spindles in the ratio of one molecule of VLB to two of tubulin with formation of cytoplasmic inclusion bodies ("microtubule crystals") (Owellen et al., 1974). This binding results in disappearance of complete spindles and inhibition of DNA and RNA and hence protein synthesis.

Carcinogenic effects: The literature has been summarized (IARC, 1981). No evidence of carcinogenicity of VLB has been reported, and where carcinogenicity in humans has been claimed this has been in patients under treatment with a combination of VLB with radiation and/or other antineoplastics, some of which were recognized carcinogens.

Mutagenic and teratogenic effects: VLB is not mutagenic in the Ames test (Seino et al., 1978; Pak et al., 1979). However, it is strongly embryotoxic and teratogenic in the chick (Cros et al., 1965), rat (DeMyer, 1964), mouse (Joneja and LeLiever, 1974), and hamster (Ferm, 1963).

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash with soap and water. Skin should not be rinsed with organic solvents. Since VLB acts as a vesicant on skin exposure, avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician. For treatment of skin exposure see Door and Alberts (1985).

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